

**REMARKS**

**I. Substance of the Interview Statement**

Applicants thank the Examiner and the Examiner's Supervisor for their time and consideration of the above-identified application in the August 24, 2010, telephone interview with Applicants' representative. During the interview, the participants discussed the outstanding rejections, the relevant references, and proposed amendments to the claims. No agreement with respect to the claims was reached.

**II. Response to Claim Rejections Under 35 U.S.C. § 103**

*A.* Claims 1-21 and 23-24 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sawhney (U.S. Patent No. 6,632,457; "D1") in view of Jeong et al. (U.S. Patent No. 6,841,617; "D2").

*B.* Claim 22 has been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sawhney in view of Jeong et al. and Fowers et al. (U.S. Patent No. 6,592,899; "D3").

These rejections are respectfully traversed.

As previously noted in the response filed April 20, 2010, one of ordinary skill in the art would appreciate that D1 tried to propose a two-phase hydrogel system to control the release rate. During preparation, D1 used oil-in-water-in oil with macromer polymerized in the outside water phase to form the system. Basically, the oil-in-water-in-oil double emulsions are easily broken, the oil phase inside the water phase during emulsification. At the same time, some hydrophobic substance may partition to the outside oil phase or accumulated on the outside surfaces of hydrogel microspheres once the hydrogel microspheres become solid through polymerization. As a result, the outside surface-associated hydrophobic substance may release very quickly and result in a burst effect.

D1 states that "The development of compositions and methods to provide controlled release delivery of relatively low molecule weight drugs presents the following challenges: the delivery matrix needs to be safe and absorbable; drug release should be controlled and sustained, while being free from burst effects; and the devices should be simple to fabricate so as to prevent denaturation of sensitive entrapped drugs." (Column 2, lines 41-44). This paragraph in D1 describes the challenges when you are skilled and experienced in this field. The challenges are

really difficult and not easy to overcome. For example, D1 did not show any data demonstrating avoidance of the burst effect. Also there is no data in D1 demonstrating avoidance of denaturation of sensitive entrapped drugs in the system if polymerization is used, or demonstrating the feasibility of using a non-polymerized hydrogel in this system. It was well known that non-polymerized hydrogels are sensitive to the gelling environment. A person of ordinary skill in the art would not have expected that a non-polymerized hydrogel could form gel when a few of oil phase existed in the system. Based on the structure and mechanism taught in D1, the reference system would not be able attain release "free of burst effect." The challenges described in D1 do not mean the reference invention can overcome the challenges.

With regard to the additional references cited by the Examiner, Applicants note that when the polymer proposed by D2 or D3 and the other available thermal sensitive hydrogels was used alone, the drug delivery system showed a burst effect due to high percentage of water content in the solidified depot. Burst effect is well known as a disadvantage of this kind of delivery system. In contrast, as noted in the present specification at page 19, the time release was extended by three fold and the burst release was also reduced in the present system. The unique combination of properties exhibited by the present systems are clearly set forth in the specification and these are not suggested by the prior art. The test data in the specification is evidence of the patentability of the claimed subject matter which must be taken into consideration in evaluating the patentability of the claimed subject matter. Rebuttal evidence and arguments can be presented in the specification, *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995), by counsel, *In re Chu*, 66 F.3d 292, 299, 36 USPQ2d 1089, 1094-95 (Fed. Cir. 1995).

Taken together, the delivery systems based on D1, D2 and D3 alone cannot avoid the burst effect. A person of ordinary skill in the art would not have reasonably predicted that combining two delivery systems with burst releasing can improve burst effect. However, in the present invention, we conducted a series of experiments and found the unexpected improvement to reduce burst effect by thermal gelling emulsion system.

In addition, D1 system cannot be applied for the other thermal gelling hydrogel system (gelling temperature close to physiological temperature). Basically, the concept of D1 is totally unable to be combined with thermogelling hydrogel to constitute the similar system as presently claimed.

Finally, Applicants submit herewith four representative review papers that support the argument that the burst effect always occurs in the polymer microsphere system because drugs may reside on or close to the surface of the microsphere during emulsion-preparation. As detailed in the review papers, a person of ordinary skill in the art would have predicted that Sawhney's microspheres would exhibit a burst effect. It would also have been reasonable for a skilled person to expect that a burst effect must occur in Sawhney's system even when combined with Jeong's hydrogel. See also the Declaration Under 37 C.F.R. § 1.132 of Dr. Pei Kan, submitted herewith. Therefore, the present invention provides unexpected results.


In view of the above, Applicants respectfully request reconsideration and withdrawal of these rejections.

#### CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions related to this response, or the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney at the below-listed telephone number concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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